INTER-SUBJECT VARIABILITY OF RESTING STATE BRAIN ACTIVITY EXPLORED USING A DATA AND MODEL-DRIVEN APPROACH IN COMBINATION WITH EEG-FMRI

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ABSTRACT

In this paper, we use co-registered EEG-fMRI during rest to investigate inter-subject-variability of BOLD signals in comparison with alpha-BOLD statistical parametric maps.
A hierarchical clustering algorithm is used to detect spatial patterns of voxels showing correlated activity. The general-linear model is used to determine which of the identified patterns correlates significantly to the spontaneous variations of the alpha rhythm.
For all sixteen subjects except one, the clustering of BOLD signal yielded very consistent regions wich included areas belonging to the "default mode" network and the neuronal networks involved in the generation of the alpha and mu rhythms. Furthermore, the BOLD clusters showed more consistency amongst subjects than the Alpha-BOLD statistical parametric maps obtained on a voxel-by-voxel basis.
It is suggested that the larger inter-subject variability observed in the Alpha-BOLD statistical parametric maps when compared to the BOLD clusters is related to the individual variations in the EEG.

Index Terms— Electroencephalography, magnetic resonance imaging, hierarchical, clustering methods

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) [1] has been used to study brain activity since the beginning of the nineties. When the goal is to find the brain areas that are involved in a given task voxels with time series that are correlated to the task paradigm are detected. To accomplish this, a *model driven* approach is used where the time series of each voxel is modeled using the General Linear Model (GLM) [2] and the regression coefficients are tested for statistical significance in order to determine those voxels where there is a significant model effect. In contrast, when the goal is to study the resting state brain activity, there is no model since the timing of the events of interest is unknown. Therefore, in resting state fMRI a *data driven* approach is applied to obtain a simplified data representation of the raw data that attains data reduction. Several data driven methods have been used to study resting state fMRI data: functional connectivity MR imaging (fcMRI) [3], Clustering [4], or Independent Component Analysis (ICA) [5].
In recent years, the co-registration of EEG and fMRI has been used to study spontaneous brain activity [6], amongst which the correlation between the spontaneous variations of the alpha rhythm and BOLD. It has been shown that there is a negative correlation between the alpha rhythm and the BOLD signal in cortical regions including e.g. the visual cortex or the pre- and post-central gyrus whereas positive correlations were found in the thalamus. These findings confirmed the generally accepted idea that the alpha rhythm is characteristic of the brain resting state [7]. In [8], though the general findings mentioned above were confirmed, considerable inter-subject variability in the statistical parametric maps (SPMs) of the Alpha-BOLD correlation was found. However [9] it was found that the hemodynamic response function (HRF) at specified points of interest is generally reproducible over subjects. EEG has revealed the main characteristics of the alpha rhythm. Although some of these characteristics show great inter-subject consistency, there are also many others (e.g. peak frequency, amplitude or reactivity to presence/absence of visual stimuli) that are inconsistent amongst subjects. In this paper the possibility that the inter-subject variability of the Alpha Rhythm-BOLD SPMs is, at least in part, a manifestation of the inter-subject variation of the alpha rhythm is tested. For that we propose to extend the data driven approach to fMRI data as preparatory step before the GLM in order to study the inter-subject variability of the BOLD signal. In addition,

advantage is taken of the simultaneous recording of the EEG to estimate the spontaneous variations of the alpha rhythm and to correlate these to the BOLD signal. In this way, we provide an interpretation of the components derived from the BOLD signals that is based on the EEG. Finally, the application of a data-driven method to fMRI data allows for data-reduction with the consequent reduction in the number of statistical tests and the simplification of statistical group analysis.

2. MATERIALS AND METHODS

2.1. Subjects

Co-registered EEG-fMRI data were acquired from 16 healthy subjects (7 males, mean age 27, ± 9 years) while they lay rested in the scanner without falling asleep. These data were the same as presented in [9]. Furthermore, an additional data set was recorded for subject 16.

2.2. Acquisition of EEG and fMRI data

The EEG was acquired using an MR compatible EEG amplifier (SD MRI 64, MicroMed, Treviso, Italy) and a cap providing 64 Ag/AgCl electrodes positioned according to the extended 10-20 system. For each subject, functional and anatomical images were acquired on a 1.5 T MR scanner (Magnetom Sonata, Siemens, Erlangen, Germany). Further details can be found in [9].

2.3. Analysis of EEG data

EEG data was corrected for gradient and pulse artifacts using an algorithm developed in-house described in [10].
Data were subdivided in 600 trials of 3 sec each, corresponding to each of the recorded fMRI volumes. Data was re-referenced to average reference.
A spectrogram based on FFT was computed for each channel these were afterwards averaged over occipital leads (O1, O2, POz, PO3, PO4, PO7, PO8, and two additional electrodes positioned between P5 and PO3, and between P6 and PO4, respectively). The alpha band power variations were obtained by averaging the power within an interval of 2 Hz around the frequency corresponding to maximum alpha band power. Outliers in the alpha power time series were excluded from further computations.

2.4. Analysis of fMRI data

The first EPI scan was automatically matched to the anatomical scan. EPI images were afterwards motion corrected and the motion parameters were later used in the correlation analysis between the BOLD signal and the power variations of the alpha rhythm. Motion corrected images were then smoothed using a Gaussian kernel with a standard deviation parameter of 5 mm. For further details, see [9].

2.5. Data pre-processing

In order to explore the inter-subject variability of the BOLD signals, we applied the hierarchical clustering algorithm described in [11]. In order to decrease the computational burden, a mask was applied to the fMRI data in order to limit the analysis to those voxels lying within the brain and the scan was spatially downsampled by a factor of 8. Several confounders were projected away from the BOLD signal, namely motion and heart beat regressors as well as a constant and a trend according to:

$$\mathbf{x_p}=(\mathbf{I_N}-\mathbf{S}(\mathbf{S^T S})^{-1}\mathbf{S^T})\mathbf{x} \qquad (1)$$

where
$\mathbf{x_p}$ is the N×1 column vector containing the projected BOLD time series;
$\mathbf{x}$ is the N×1 column vector containing the unprojected BOLD time series;
N is the number of time points;
$\mathbf{I_N}$ is the N×N identity matrix;
$\mathbf{S}$ is N×L matrix containing the confounders in columns,
L is the number of confounders.

2.6. Clustering

The clustering algorithm was initialized with a table containing the distances between the BOLD time series of any two voxels. The time series were regarded as vectors in R^N and Euclidean distances between normalized vectors were used.
The selection of clusters of interest was guided by their potential functional meaning and it as directed towards clusters containing areas where the generators of the alpha rhythm are located or towards regions belonging to the "default-mode network". Four reference points were defined consistently for all subjects. Within the mid-sagittal plane three points were placed in the visual cortex, superior parietal lobe and orbitofrontal cortex respectively. The fourth point was placed in the left central sulcus. Only the clusters containing at least one of these points were selected for further analysis.

2.7. Correlating EEG to fMRI on a cluster-wise basis

In order to provide an interpretation of the spatial patterns identified by the clustering algorithm, the fMRI signal corresponding to each cluster was correlated to the alpha rhythm according to the GLM as in [9]. Briefly, the BOLD signal x in each voxel was modeled according to:

$$\mathbf{x}=\mathbf{R}\boldsymbol{\alpha}+\mathbf{S}\boldsymbol{\beta}+\boldsymbol{\eta} \qquad (2)$$

where

R is the N×I matrix containing the regressors of interest columns;

I is the number of regressors of interest;

α is the I×1 column vector and it contains the hemodynamic response function

β is the L×1 columns vector containing the regression coefficients associated with the confounders;

η is the N×1 column vector containing Gaussian noise.

The regressors of interest were shifted versions of the alpha power time series and the shifts ranged from -6 to 21 seconds. The confounders were those used in (1). In (2), x was the BOLD time series corresponding to the center of the clusters (i.e. the average BOLD time series computed from all elements belonging to the cluster), matrix R contained the shifted versions of the spontaneous variations of the alpha rhythm power and α was the alpha response function (ARF) [9]. Using (2) the correlation between the alpha rhythm and the BOLD time series of each of the selected clusters was determined for each subject. The statistical significance of each correlation over all subjects was obtained by controlling the false detection rate (FDR) at a level of 0.001. It should be stressed that due to the limited amount of tests per subjects, the control of the FDR over the total number of tests could simply be used to obtain group results.

For comparison, the alpha rhythm was also correlated to BOLD on a voxel-by-voxel basis, similar to [9] and with FDR=0.01.

3. RESULTS

A typical example of the derived clusters is presented in figs. 1 and 2.

In fig. 1, a typical example of the *Occ* cluster, represented in blue, and the *SomMot* cluster, represented in red, are shown for subject 4. The *Occ* cluster includes the occipital lobe (cuneus) and encroaches the superior regions of the cerebellum. The *SomMot* cluster includes the pre- and post-central gyrus, the superior temporal lobe as well as the inferior parietal lobe. For two subjects 3 and 14, only one cluster containing both pre- and post-central gyros as well as the visual cortex was found. Finally, for subject 10, only two clusters were derived. One of these was quite large and indistinct including most of the brain.

Figure 2 a typical example of, the *OrbFr* cluster, represented in light blue and the *SupPar* cluster, represented in green. In general, the *OrbFr* cluster includes the inferior and middle temporal gyrus as well as the uncus.

The *SupPar* cluster contains the anterior and posterior cingulate, the pre-cuneus as well as the superior and medial frontal gyrus. For subjects 2, 7 and 16 only one cluster was identified including the regions associated with the *OrbFr* and *SupPar* clusters.

In fig. 3 the statistical parametric maps (SPMs) resulting from correlating the spontaneous variations of the alpha rhythm with the BOLD signal, on a voxel-by-voxel basis and

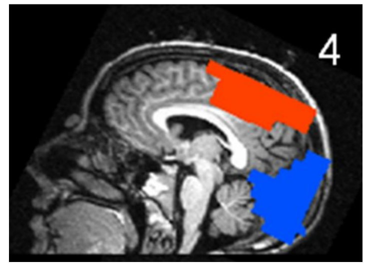

Fig. 1 – See text.

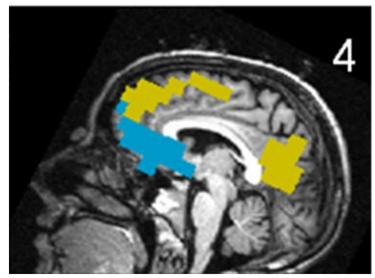

Fig. 2 – See text.

with a significance level corresponding to FDR=0.01 are shown for some typical subjects. Correlation values range from 0.23 to 0.70. Increasing correlation values are color-coded from dark red to white. These results show that there is considerable inter-subject variation in the correlation distribution, thus confirming what has been reported in [8]. In fact, if for some subjects (e.g. subjects 5, 9 and 13) extensive areas correlated to BOLD are found, for other subjects (e.g. subjects 3, 6, 10 and 15) hardly any significant correlation is found. The comparison of figs 1a, 1b and 3 shows that there is much more inter-subject variability in the SPMs corresponding to the correlation between alpha rhythm and BOLD than in the clusters containing voxels with correlated times series.

In Table 1, the values of the correlation between the spontaneous variations of the alpha rhythm and the average BOLD signal corresponding to each of the selected clusters for each subject are presented. The values with the symbol † are not significant at the chosen significance level. For almost all subjects the four clusters mentioned above, i.e. the *Occ*, *SomMot*, *OrbFr* and *SupPar* clusters, were considered. In the table, this is represented by merging the entries corresponding to those clusters that are not separated and/or by attributing the same background color to the corresponding entries. The columm *EEG-fMRI SPMs* refers to the statistical significance (*S*-significant, *NS*-Nonsignificant) of the Alpha-BOLD SPMs on a voxel-by-voxel basis.

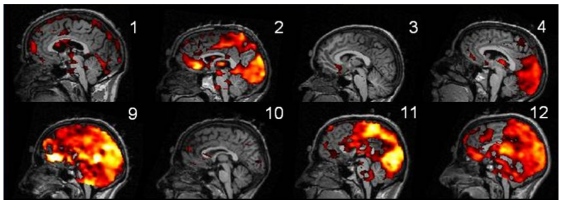

Fig. 3 – See text.

<table>
<tr><th>Subject</th><th>Occ</th><th>SomMot</th><th>SupPar</th><th>OrbFr</th><th>EEG-fMRI SPMs</th></tr>
<tr><td>1</td><td>0.233</td><td colspan="2">0.366</td><td>0.285</td><td>NS</td></tr>
<tr><td>2</td><td>0.566</td><td>0.522</td><td colspan="2">0.582</td><td>S</td></tr>
<tr><td>3</td><td colspan="2">0.266</td><td>0.249</td><td>0.196†</td><td>NS</td></tr>
<tr><td>4</td><td>0.477</td><td>0.300</td><td>0.266</td><td>0.375</td><td>S</td></tr>
<tr><td>5</td><td>0.724</td><td>0.723</td><td>0.516</td><td>0.548</td><td>S</td></tr>
<tr><td>6</td><td>0.279</td><td>0.246</td><td>0.153†</td><td>0.159†</td><td>NS</td></tr>
<tr><td>7</td><td>0.417</td><td>0.354</td><td colspan="2">0.240</td><td>S</td></tr>
<tr><td>8</td><td>0.386</td><td>0.379</td><td>0.387</td><td>0.340</td><td>NS</td></tr>
<tr><td>9</td><td>0.513</td><td>0.513</td><td>0.513</td><td>0.629</td><td>S</td></tr>
<tr><td>10</td><td colspan="3">0.356</td><td>0.318</td><td>NS</td></tr>
<tr><td>11</td><td>0.590</td><td>0.529</td><td>0.295</td><td>0.414</td><td>S</td></tr>
<tr><td>12</td><td>0.505</td><td>0.401</td><td>0.456</td><td>0.440</td><td>S</td></tr>
<tr><td>13</td><td>0.594</td><td>0.525</td><td>0.488</td><td>0.275</td><td>S</td></tr>
<tr><td>14</td><td colspan="2">0.279</td><td>0.287</td><td>0.209</td><td>S</td></tr>
<tr><td>15</td><td>0.277</td><td>0.254</td><td>0.283</td><td>0.240</td><td>NS</td></tr>
<tr><td>16</td><td>0.229</td><td>0.276</td><td colspan="2">0.115†</td><td>NS</td></tr>
</table>

Table I – See text.

Results show that for all subjects, the alpha rhythm correlates significantly to the BOLD signal of the *Occ* and *SomMot* clusters. This applies even to those subjects for who hardly any significant correlation was found on a voxel-by-voxel basis (see e.g. Fig.4, subjects 1, 3 and 10 and last column of Table 2). The alpha rhythm also correlates to the *OrbFr* and *SupPar* clusters although in general, the correlation values tend to be lower than those found for the *Occ* and *SomMot* clusters.

4. DISCUSSION AND CONCLUSIONS

One main conclusion is that an optimized strategy to obtain reliable results regarding the correlation between EEG (Alpha rhythm) signals and BOLD is to first apply hierarchical clustering to define a few relevant ROIs, and thereafter to compute correlations restricted to these ROIs. In this way we obtain and enhanced statistical power by having better signal-to-noise ratios and by reducing the dimensionality of the multiple comparisons problem. A second main conclusion of this study is that the inter-subject variability of the spatial distribution of clusters of voxels with correlated BOLD signals during rest is much less pronounced than that of the corresponding EEG-fMRI SPMs. Thus, the latter may be a consequence of the variability associated with the resting state EEG.

It is shown that clusters of voxels defining extensive brain networks correlate to the alpha rhythm. This finding supports the idea that the latter is a manifestation of a dynamic process which regulates a large group of integrative brain functions [12] and therefore the derived clusters of voxels can be interpreted as regions associated with these functions.

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